General Psychiatry

# Adjunctive aripiprazole for antipsychotic-related hyperprolactinaemia in patients with first-episode schizophrenia: a meta-analysis

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## ABSTRACT

**Background** Hyperprolactinaemia is a common antipsychotic (AP)-induced adverse effect, particularly in female patients.

**Aims** This meta-analysis examined the efficacy and safety of adjunctive aripiprazole in preventing AP-related hyperprolactinaemia in patients with first-episode schizophrenia.

**Methods** PubMed, PsycINFO, EMBASE, Cochrane Library, WanFang and China Journal Net databases were searched to identify eligible randomised controlled trials (RCTs). Primary outcomes were the reductions of serum prolactin level and prolactin-related symptoms. Data were independently extracted by two reviewers and analysed using RevMan (V.5.3). Weighted/standardised mean differences (WMDs/SMDs)±95% CIs were reported.

**Results** In the five RCTs (n=400), the adjunctive aripiprazole (n=197) and the control groups (n=203) with a mean of 11.2 weeks of treatment duration were compared. The aripiprazole group had a significantly lower endpoint serum prolactin level in all patients (five RCTs, n=385; WMD: −50.43 ng/mL (95% CI: −75.05 to −25.81), p<0.00001; $I^2$=99%), female patients (two RCTs, n=186; WMD: −22.58 ng/mL (95% CI: −25.67 to −19.49), p<0.00001; $I^2$=0%) and male patients (two RCTs, n=127; WMD: −68.80 ng/mL (95% CI: −100.11 to −37.49), p<0.0001). In the sensitivity analysis for the endpoint serum prolactin level in all patients, the findings remained significant (p<0.00001; $I^2$=96%). The aripiprazole group was superior to the control group in improving negative symptoms as assessed by the Positive and Negative Syndrome Scale (three RCTs, n=213; SMD: −0.51 (95% CI: −0.79 to −0.24), p=0.0002; $I^2$=0%). Adverse effects and discontinuation rates were similar between the two groups.

**Conclusions** Adjunctive aripiprazole appears to be associated with reduced AP-induced hyperprolactinaemia and improved prolactin-related symptoms in first-episode schizophrenia. Further studies with large sample sizes are needed to confirm these findings.

## INTRODUCTION

Hyperprolactinaemia caused by antipsychotics (APs) is a serious and unwanted adverse effect in patients with schizophrenia.[1 2] With the rates up to 86%,[3] it is closely related to the dopamine D2 receptor gene Taq1A genotype.[4]

There have been several treatment strategies recommended to prevent or alleviate hyperprolactinaemia in clinical practice although some remain controversial because (1) the use of the lowest effective AP dose may increase the risk of relapse during maintenance treatments;[5] (2) switching to other APs with a lower risk of hyperprolactinaemia could be associated with some other adverse effects, such as sedation and metabolic syndrome;[6] (3) adding a dopamine agonist, such as cabergoline, may result in abnormal involuntary movements and aggravated psychosis;[7 8] (4) the use of metformin, which may bring benefits to some hyperprolactinaemic patients,[9 10] may be associated with gastrointestinal reactions;[11] and (5) the evidence for the use of paeoniae–glycyrrhiza decoction, a herbal medicine formula consisting of paeonia and glycyrrhiza radices (Shaoyao-Gancao-Tang in Chinese and Shakuyaku-Kanzo-To in Japanese, TJ-68), is still lacking.[7 12–14]

Emerging evidence has found that aripiprazole, a partial agonist of dopamine D2 receptors,[15 16] could effectively reduce prolactin level and increase the rate of prolactin normalisation, and even improve prolactin-related symptoms in patients with AP-related hyperprolactinaemia.[2 17 18] In addition, it would appear that adjunctive aripiprazole is one of the safest strategies to improve hyperprolactinaemia induced by APs.[19]

To date, several randomised controlled trials (RCTs)[20–24] of aripiprazole as an adjunct treatment for AP-induced hyperprolactinaemia have been conducted in first-episode patients with schizophrenia, but the results are inconsistent. An earlier meta-analysis focusing on both patients with first-episode and chronic schizophrenia found superiority of adjunctive aripiprazole over placebo in the improvement of AP-related hyperprolactinaemia.[18] To date, however, no meta-analysis or systematic review exclusively examining the effect of adjunctive aripiprazole in preventing AP-related hyperprolactinaemia in first-episode schizophrenia was published. We thus conducted this meta-analysis of RCTs in patients with first-episode schizophrenia to evaluate the efficacy and safety of aripiprazole as an additional treatment for hyperprolactinaemia induced by AP.

## METHODS

### Types of studies

Based on the *PICOS* acronym as recommended by the previous meta-analyses[25 26], the following selection criteria of this meta-analysis were presented: Participants (*P*): adult patients (without restriction in setting, gender and ethnicity) with first-episode schizophrenia based on any diagnostic criteria. First episode was defined as first onset of psychotic symptoms. Intervention (*I*): the combination of APs and aripiprazole. Comparison (*C*): the combination of APs and placebo or AP monotherapy. Outcomes (*O*): the primary outcome was the reduction of serum prolactin level; key secondary outcomes included (1) the improvement of prolactin-related symptoms (oligomenorrhoea, amenorrhoea and galactorrhoea recovery), (2) improvement of psychotic symptoms as assessed by the Positive and Negative Syndrome Scale (PANSS)[27] or the Brief Psychiatric Rating Scale (BPRS),[28] (3) tolerability and safety: discontinuation rate and adverse effects as assessed by the Treatment Emergent Symptom Scale.[29] Study design (*S*): RCTs (no restriction in treatment duration) reporting prolactin-related symptoms or serum prolactin levels with meta-analysable data. We excluded observational studies, case reports/series, conference articles, non-randomised studies, animal studies, meta-analyses and systematic reviews.

### Study selection

A systematic search, in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement,[30] was performed in English (PubMed, EMBASE, PsycINFO, Cochrane Library databases) and Chinese databases (WanFang and China Journal Net databases) for RCTs evaluating adjunctive aripiprazole for hyperprolactinaemia induced by AP in patients with first-episode schizophrenia from inception to 1 July 2019. The keywords used for the searches included (aripiprazole OR abilify) AND (hyperprolactinemia OR gynecomastia OR galactorrhea OR amenorrhea OR oligomenorrhea OR menstrual irregularities OR prolactin) AND (schizoaffective disorder OR schizophreniform OR Schizophrenic Disorder OR Disorder, Schizophrenic OR Schizophrenic Disorders OR Schizophrenia OR Dementia Praecox) AND (first episode OR early phase OR early-phase OR treatment-naïve OR naïve OR untreated OR undiagnosed OR first diagnosed OR first diagnosis). The bibliographies of published relevant reviews or meta-analyses[2 18] also were hand-searched for additional studies.

### Data extraction

Two independent reviewers identified, checked and extracted data of the included studies. Inconsistencies were resolved by consensus involving a third reviewer. If the same data were reported in more than one RCT, only the RCT with complete data was included for analyses. Authors were contacted by email in order to obtain missing or more information if necessary.

### Statistical methods

All meta-analytic data were performed using RevMan (V.5.3) (http://www.cochrane.org) following the recommendations of the Cochrane Collaboration. A random-effect model[31] was used in all cases due to heterogeneity in methodology, treatment duration, study size, sampling and doses of aripiprazole. For dichotomous and continuous outcomes, risk ratios and weighted and standardised mean differences (WMDs/SMDs) with their 95% CIs were reported, respectively. There was a heterogeneous result for meta-analytic data when $I^2$ values were greater than 50% or p value <0.1 in the *Q* statistics.[32] For primary outcomes, we sought reasons for heterogeneity by conducting a sensitivity analysis by removing two outlying (SMD <−5.0) studies.[20 22] Publication bias was assessed using the funnel plots and Egger's Regression Intercept.[33] All analyses were two tailed, with the significance level set at 0.05.

### Assessment of study quality

The quality of included RCTs were independently assessed by two reviewers (X-HY and D-BC) using Cochrane risk of bias.[34] Following the methodology of other studies,[35 36] the Jadad scale[37] was also used to assess the quality of each study. Furthermore, the criteria of high and low quality of the included studies were defined as Jadad scores ≥3 and <3, respectively.[35 36] Additionally, the quality of overall evidence of primary and secondary outcome measures of adjunctive aripiprazole for hyperprolactinaemia was assessed using the grading of recommendations assessment, development and evaluation (GRADE) system.[38 39]

## RESULTS

### Results of the search

A total of 872 potentially relevant articles in the initial database search (870 trials) and other sources (two trials) were ascertained (figure 1). After removing duplicate articles (156 trials), and reading the titles or abstracts

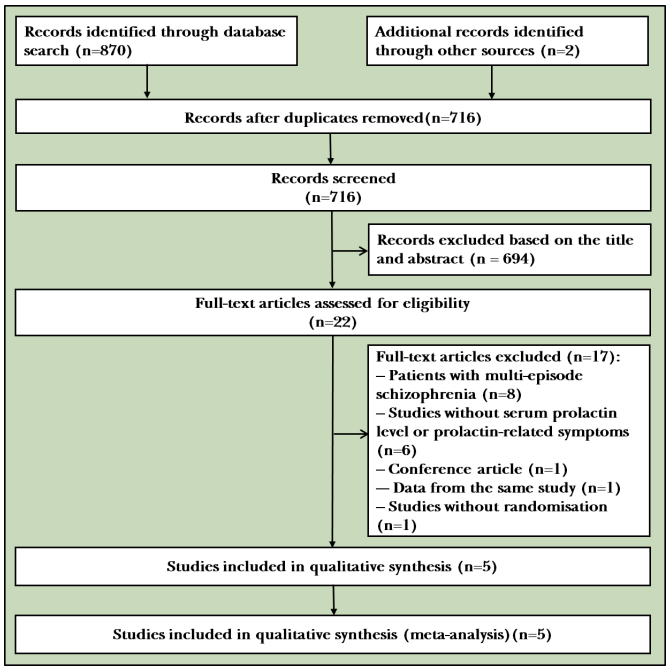


**Figure 1** PRISMA flowchart. RCT, randomised controlled trial.

(694 trials) and reviewing full texts (17 trials), finally, five RCTs were eligible and analysed.

### Study characteristics

All five RCTs (n=400) included double-blinded (one RCT, n=80), single-blinded (one RCT, n=72) and open-label trials (three RCTs, n=248) and compared the adjunctive aripiprazole (n=197) and the control groups (n=203). The mean of the treatment duration was 11.2 weeks (range, 8–24 weeks) (table 1). All included RCTs were conducted in China.

### Patient characteristics

Only two RCTs[20 23] reported mean age with 36.7 years (range, 30.5–42.9 years) (table 1). The percentage of men was 50% (range, 0%–100%) in four RCTs with available data,[20 21 23 24] and illness duration was 15.3 (range, 4.5–26) months in two RCTs with available data.[20 23]

### Treatment characteristics

The mean dosage of aripiprazole dosage was 7.5 mg/day (range, 2.5–10 mg/day) in four RCTs with available data. Furthermore, baseline APs included amisulpride (one RCT), olanzapine (one RCT), risperidone (two RCTs) and sulpiride (one RCT).

### Quality assessment

Three RCTs reported randomisation methods with a specific description and the remaining were rated as unclear (online supplementary figure 1). The Jadad score ranged from 1 to 4 (mean=2.6) (table 1). Two studies (40%) were classified as low quality and the others were high quality (60%), respectively. The quality of evidence presented for nine outcome measures, based on the GRADE approach, ranged from 'very low' (12.5%), 'low' (50.0%) to 'moderate' (37.5%) (online supplementary table 1).

### Treatment efficacy

The aripiprazole group had a significantly lower endpoint serum prolactin level in all patients (five RCTs, n=385; WMD: −50.43 ng/mL (95% CI: −75.05 to −25.81), p<0.00001; $I^2$=99%, figure 2), in female patients (two RCTs, n=186; WMD: −22.58 ng/mL (95% CI: −25.67 to −19.49), p<0.00001; $I^2$=0%, figure 2) and in male patients (two RCTs, n=127; WMD: −68.80 ng/mL (95% CI: −100.11 to −37.49), p<0.0001, figure 2) when compared with the control group.

The results remained significant after removing two outlying studies[20 22] regarding endpoint serum prolactin level in all patients (three RCTs, n=248; WMD: −39.39 ng/mL (95% CI: −56.63 to −22.15), p<0.00001; $I^2$=96%).

Due to the limited number of RCTs, subgroup and meta-regression analyses, and publication bias could not be examined.

### Psychiatric symptoms

Meta-analyses of PANSS negative symptoms (three RCTs, n=213; SMD: −0.51 (95% CI: −0.79 to −0.24), p=0.00002; $I^2$=0%, figure 3) showed a significant superiority of the adjunctive aripiprazole group over the control group. However, meta-analyses of total scores of PANSS (four RCTs) and BPRS (one RCT) (five RCTs, n=385; SMD: −0.32 (95% CI: −0.64 to 0.00), p=0.05; $I^2$=60%, figure 3) and PANSS positive symptoms (three RCTs, n=213; SMD: −0.08 (95% CI: −0.58 to 0.43), p=0.76; $I^2$=71%, figure 3) did not show significant differences between the aripiprazole and the control groups.

### Adverse effects and discontinuation rates

Three RCTs reported adverse effects (table 2). Meta-analyses of any extrapyramidal symptoms (p=0.84, online supplementary figure 2) did not show significant differences between the two groups. Prolactin-related symptoms (such as amenorrhoea, oligomenorrhoea and galactorrhoea) were significantly more frequent in the control group compared with the aripiprazole group (table 2). However, nine female patients reported galactorrhoea and seven male patients reported gynecomastia in the aripiprazole group, while no female or male patients reported these two outcomes in the control group in one RCT. Other adverse effects did not significantly differ between the two groups (table 2).

Meta-analyses of all caused discontinuation did not show significant differences between the two groups (p=0.47, online supplementary figure 2).

## DISCUSSION

### Main findings

To the best of our knowledge, this was the first meta-analysis of RCTs that examined the efficacy and safety of adjunctive aripiprazole for AP-related

**Table 1** Study, patient and treatment characteristics*

| Study | Number of patients | Blinding | Analyses | Trial duration (weeks) | Setting (%) | Diagnosis (%) | Diagnostic criteria | Illness duration* (months) | Age*: years (range) | Sex*: male (%) | Control group: dose (mg/day): mean (range) | Intervention group: dose (mg/day): mean (range) | | Jadad score | Prolactin level at baseline (ng/mL) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Chen *et al* 2009 (China)[20] | T: 80<br>C: 40<br>I: 40 | DB | OC | 8† | Inpatients (100) | Sz (100), first episode | CCMD-3 | 4.5 | 30.5 (18–48) | 100 | RIS: Ø=4.0 (2–5) | RIS: Ø=4.1 (2–5) | ARI: Ø=5 (FD) | 4 | 20.52 |
| Chen *et al* 2012 (China)[21] | T: 86‡<br>C: 46<br>I: 40 | OL | OC | 8§ | Inpatients (100) | Sz (100), first episode | CCMD-3 | NR | NR (18–55) | 0 | OLA: Ø=NR (5–20) | OLA: Ø=NR (5–20) | ARI: Ø=10 (FD) | 1 | 13.88 |
| Ren and Hu 2011 (China)[22] | T: 72<br>C: 36<br>I: 36 | SB¶ | ITT | 8 | Outpatients (0) | Sz (100), first episode | ICD-10 | NR | NR (18–60) | NR | SUL: Ø=NR (400–900) | SUL: Ø=NR (400–900) | ARI: Ø=NR (NR) | 3 | 15.00 |
| Sha *et al* 2017 (China)[23] | T: 62<br>C: 31<br>I: 31 | OL | ITT | 8 | NR | Sz (100), first episode | CCMD | 26.0 | 42.9 (20–55) | 100 | AMI: Ø=NR (200–800) | AMI: Ø=NR (200–800) | ARI: Ø=2.5 (FD) | 3 | 12.69 |
| Zhou *et al* 2014 (China)[24] | T: 100<br>C: 50<br>I: 50 | OL | ITT | 24 | Both (NR) | Sz (100), first episode | CCMD-3 | NR | NR (18–40) | 0 | RIS: Ø=NR (4–6) | RIS: Ø=NR (4–6) | ARI: Ø=5 (FD) | 2 | 10.56 |

*Available data were extracted based on mean baseline value of each included trials.
†Only data receiving aripiprazole treatment were extracted.
‡Number of patients were the data from the completion of the trial because the random assignment data were not clear.
§Data were obtained by contacting with the first author.
¶Only used the placebo but it is unclear about the blinding of the rater.
. Ø, mean; AMI, amisulpride; ARI, aripiprazole; Both, in–outpatients; C, control; CCMD, China's mental disorder classification and diagnosis standard; CCMD-3, China's mental disorder classification and diagnosis standard 3rd edition; DB, double blind; FD, fixed dose; I, intervention; ICD-10, the 10th revision of the International Statistical Classification of Diseases and Related Health Problems; ITT, intent to treat; NR, not reported; OC, observed cases; OL, open label; OLA, olanzapine; RIS, risperidone; SB, single blind; SUL, sulpiride; Sz, schizophrenia; T, total.

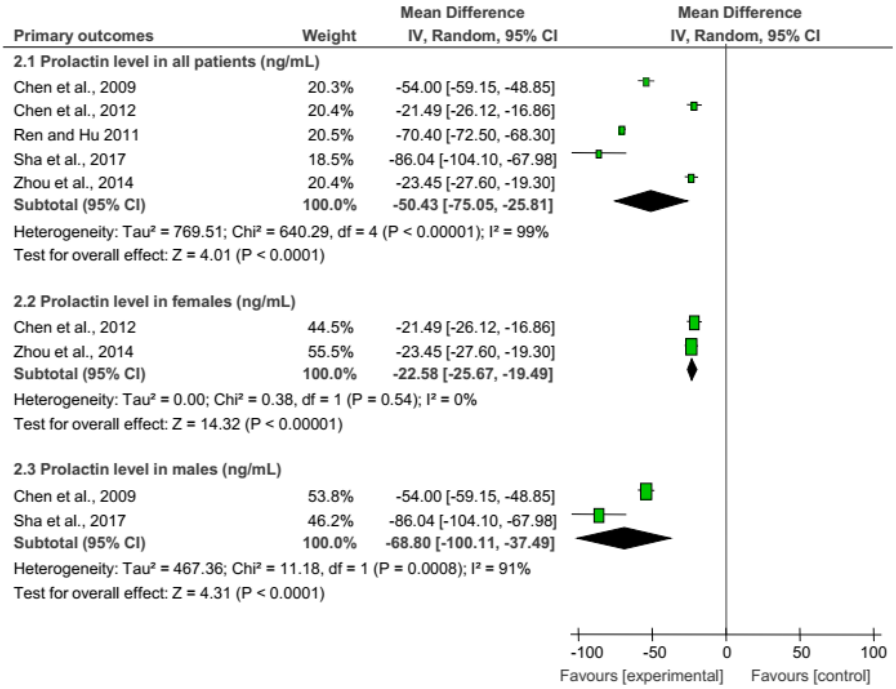


**Figure 2** Adjunctive aripiprzaole for antipsychotic-induced hyperprolactinaemia: forest plot for the serum prolactin level (ng/mL) and body weight (kg) at endpoint.

hyperprolactinaemia in patients with first-episode schizophrenia. The findings suggest that adjunctive aripiprazole could significantly reduce the level of elevated prolactin and improve prolactin-related symptoms. This adjunctive strategy appears to be safe, well-tolerated and associated with improved negative symptoms. Given that the overall quality level was rated as 'low' in reducing the level of elevated prolactin and improving negative symptoms, these findings need to be interpreted with caution.

## Limitations

The study has several limitations. First, the sample sizes were relatively small (n=400) in the five RCTs, which

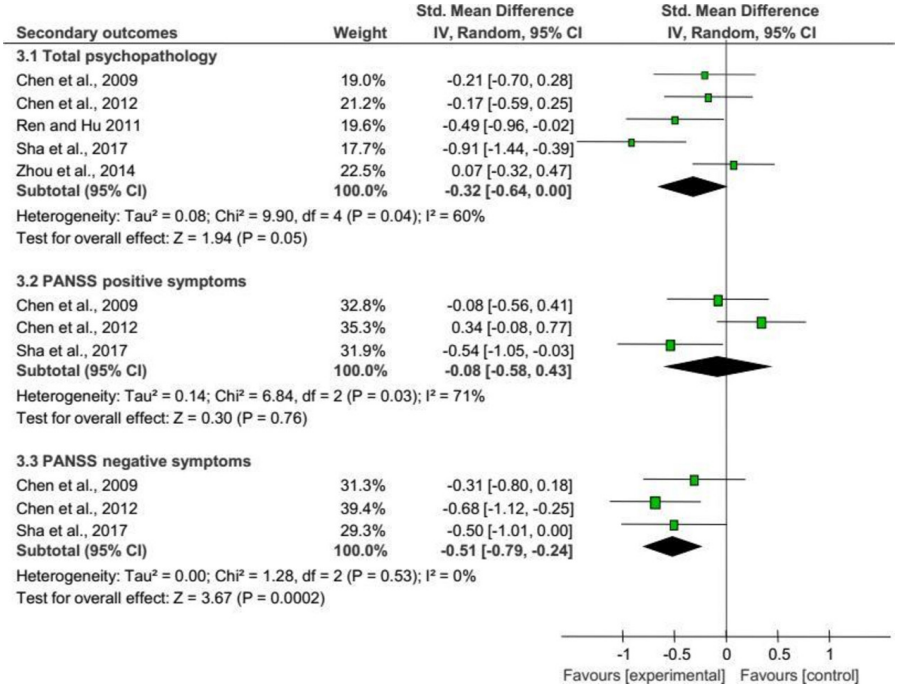


**Figure 3** Adjunctive aripiprazole for antipsychotic-induced hyperprolactinaemia: forest plot for total psychopathology assessed by the Positive and Negative Syndrome Scale (PANSS) and the Brief Psychiatric Rating Scale, PANSS positive symptom and negative symptom at endpoint.

Table 2 Adjunctive aripiprazole for antipsychotic-related hyperprolactinaemia: ADRs

| Secondary outcome | Study | Control group | | Aripiprazole group | | Findings |
|---|---|---|---|---|---|---|
| | | Total (n) | Events (n) | Total (n) | Events (n) | |
| Prolactin-related symptom* | Zhou *et al* 2014[24] | 50 | 28 | 50 | 4 | p<0.05 |
| Any extrapyramidal related with adverse effect† | Zhou *et al* 2014[24] | 50 | 22 | 50 | 24 | NS |
| Galactorrhoea (female) | Ren and Hu 2011[22] | 16 | 9 | NR | 0 | NA |
| Gynecomastia (male) | Ren and Hu 2011[22] | 20 | 7 | NR | 0 | NA |
| Akathisia | Ren and Hu 2011[22] | 36 | 0 | 36 | 1 | NS |
| Any extrapyramidal related with adverse effect | Ren and Hu 2011[22] | 36 | 2 | 36 | 0 | NS |
| Insomnia | Ren and Hu 2011[22] | 36 | 0 | 36 | 2 | NS |
| Tremor | Chen *et al* 2009[20] | 40 | 4 | 40 | 4 | NS |
| Dry mouth | Chen *et al* 2009[20] | 40 | 3 | 40 | 3 | NS |
| ECG abnormality | Chen *et al* 2009[20] | 40 | 4 | 40 | 3 | NS |
| Dizziness | Chen *et al* 2009[20] | 40 | 3 | 40 | 2 | NS |
| Tachycardia | Chen *et al* 2009[20] | 40 | 6 | 40 | 8 | NS |
| Anxiety | Chen *et al* 2009[20] | 40 | 5 | 40 | 4 | NS |
| Constipation | Chen *et al* 2009[20] | 40 | 4 | 40 | 6 | NS |
| Elevated liver enzymes | Chen *et al* 2009[20] | 40 | 6 | 40 | 5 | NS |
| Hypersalivation | Chen *et al* 2009[20] | 40 | 6 | 40 | 8 | NS |
| Hyperglycaemia | Chen *et al* 2009[20] | 40 | 2 | 40 | 3 | NS |

*Included amenorrhoea, oligomenorrhoea, galactorrhoea, etc.
†Included akathisia, tremor, oculogyric crisis, etc.
ADR, adverse drug reaction; NA, not applicable; NR, not reported; NS, not significant.

hinders the ability to conduct more comprehensive data analyses, such as subgroup and meta-regression analyses. Second, three RCTs were classified as high quality using the Jadad scale[37] and three RCTs reported randomisation methods with a specific description using the Cochrane risk of bias,[34] but the quality of 50% of the overall evidence was classified as 'low' quality based on the GRADE approach.[38 39] However, low-quality evidence could still result in strong recommendations according to Guyatt *et al*'s suggestion.[40] Third, the significant heterogeneity ($I^2$>50%) of meta-analytic results of serum prolactin level in the whole sample may be attributed to different methodology, study sizes, sampling, antipsychotic doses and treatment duration across studies. However, the results remained the same after a sensitivity analysis by removing two outlying studies was conducted. Finally, all included studies were conducted in China and published in Chinese. Therefore, the findings of the current study warrant confirmation in other countries.

## Implications

APs, such as haloperidol or risperidone, increase prolactin secretion through dopamine-blocking actions in the tuberoinfundibular system.[41] Antagonist activity at D2 receptors in the tuberoinfundibular system region reduces dopamine activity and then increases the risk of hyperprolactinaemia.[2] In contrast, aripiprazole is a partial dopamine agonist in conditions of low endogenous dopamine activity[15] and could suppress the elevated serum prolactin level by preventing the development of hypodopaminergia in the tuberoinfundibular system .[2]

Aripiprazole dose–response effects in reducing the elevated prolactin level could not be analysed in this meta-analysis because the aripiprazole mean doses (7.5 mg/day) were only provided in four RCTs. A prior meta-analysis[2] of five RCTs (n=663) suggested aripiprazole less than 5 mg/day could significantly decrease prolactin levels in patients with chronic schizophrenia. In addition, 2 mg/day of aripiprazole could act as a partial dopamine agonist and showed improvement of prolactin-related symptoms.[42 43] Thus, a dose of 5 mg/day appears to be a reasonable target dose for aripiprazole for AP-related hyperprolactinaemia in patients with first-episode schizophrenia, but further studies are needed to explore the optimal dose range.

Apart from its efficacy in reducing the elevated prolactin level, adjunctive aripiprazole could significantly improve negative symptoms, which is consistent with a recent published meta-analysis.[18]

## CONCLUSIONS

This meta-analysis of RCTs showed that adjunctive aripiprazole appears to be associated with reduced hyperprolactinaemia induced by AP and improved

prolactin-related symptoms in first-episode schizophrenia, which has important clinical implications for reducing the risk of AP-related hyperprolactinaemia. It may also improve prolactin-related symptoms without associated increase in adverse effects and discontinuation rates. RCTs with a larger sample size on aripiprazole for hyperprolactinaemia induced by APs in patients with first-episode schizophrenia are needed in the future.

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**Correction notice** This article has been corrected since it was first published online. The author list has been updated and amended. Affiliations have been corrected.

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